The Synthesis of 1-Phenylpropane Derivatives. IV*

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In previous papers1,2) the syntheses of several *threo* and *erythro* 1-phenyl-2-amino-1, 3-propanediol derivatives, starting from benzoyl chloride and ethylene, have been described. The steric courses which led to these stereoisomeric products have also been discussed. In this paper, the preparation of *threo* and *erythro* 1-phenyl-2-acetamido-1, 3-propanediol and related compounds starting from benzoly chloride and vinyl chloride will be reported. The synthetic processes are outlined in Fig. 1.

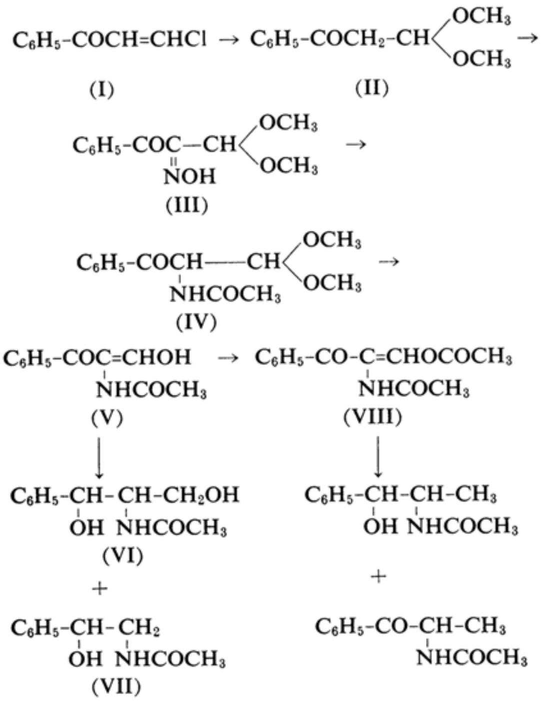

Fig. 1

The starting material, phenyl β-chlorovinyl ketone, was obtained in a 70—90% yield by a modification of Klinko's method.3) After this compound had been converted to benzoylacetaldehyde dimethy acetal (II)4) by methanolic sodium hydroxide, the product was treated with amyl nitrite in methanolic sodium methoxide.5) The isolation of the desired oximinoketone (III), which is present in the reaction mixture as a sodium salt, offered considerable difficulty, however.6) The compound III appears to be sensitive to acidic substances; neutralization with even such weak acids as acetic, phosphoric, and boric acids resulted in the formation of only an intractable mixture. After many unsuccessful attempts, the difficulty was overcome by the use of ammonium chloride as a neutralizing agent. By this procedure, the pure oximinoketone was obtained in a 76% yield. In the hope of preparing 1-phenyl-2-amino-1, 3-propanediol derivatives by the routes shown in Fig. 2, attempts were made to convert oximinoketone (III), acetoximinoketone (III′) and their reduction products IX and IX′ to the alcohols X, X′, XI, and XI′ respectively. However, the hydrolysis of the acetal group of III, III′, IX and IX′ with a variety of acids, including boric, phosphoric, and acetic acids, did not afford pure crystalline materials.

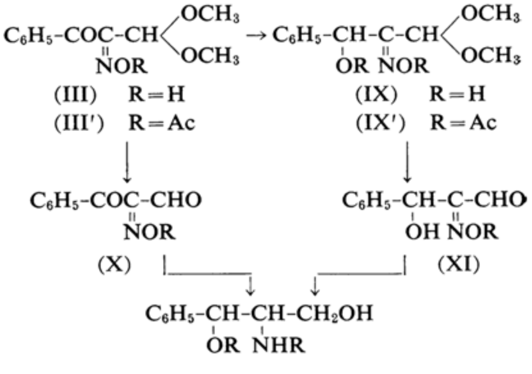

Fig. 2

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* Part III: Ref. 10b.

1) T. Matsumoto and K. Hata, *J. Am. Chem. Soc.*, **79**, 5506 (1957).

2) T. Matsumoto, H. Shirahama and T. Nishida, *J. Org. Chem.*, **27**, 79 (1962).

3) V. T. Klinko, V. A. Mikhalv and A. P. Sklodinov, *Zhur. Opschei Khim.*, **27**, 370 (1957); *Chem. Abstr.*, **51**, 15499 (1957).

4) C. C. Price and J. A. Pappalardo, *J. Am. Chem. Soc.*, **72**, 2613 (1950).

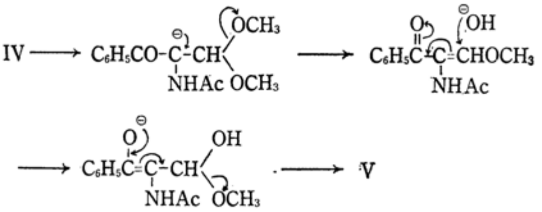
5) L. Claisen and O. Manasse, *Ber.*, **20**, 2194 (1887).

6) The reaction mixture in which oximinoketone (III) is present exhibits deep blue coloration upon the addition of an aqueous ferrous sulfate solution. On the contrary, the ferrous sulfate test for oximinoketones according to Feigl's procedure, which is performed in the presence of ammonia (F. Feigl, "Tüpfelreaktionen," Akademishe Verlagsgesellshaft, Leibzig (1938), p. 87) was negative for pure III. However, the addition of dilute ethanolic sodium ethoxide seems to provide a more sensitive method, at least for this case.

Syntheses along these lines were, therefore, abandoned.

The catalytic hydrogenation of oximinoketone (III) in 3 N methanolic hydrogen chloride in the presence of palladium was examined next. The stereospecific formation of norephedrine from α-oximinopropiophenone under similar conditions has been reported.[7] The removal of the solvent left, however, an intractable tarry material, probably formed by the hydrolysis of the acetal group by hydrogen chloride and by subsequent condensation between the aldehyde group and the newly-formed amino group. Therefore, the reaction mixture was, in the next attempt, at first neutralized by passing through ammonia. The removal of ammonium chloride by the addition of ether, the evaporation of the solvent, and the subsequent benzoylation of the residue afforded a small amount of crystals. Elemental analysis indicates that the product is dibenzoyl-1-phenyl-2-amino-3, 3-dimethoxy-1-propanol (the configuration was not examined). In a separate attempt, after the absorption of three moles of hydrogen, a small amount of water was added to effect the hydrolysis of the acetal group. The catalyst was then replaced by platinum oxide, and the hydrogenation was continued until one further mole of hydrogen had been absorbed. The benzoylation of the product afforded a compound with an elemental composition corresponding to that of a tribenzoyl derivative (m. p. 204—207°C) of 1-phenyl-2-amino-1, 3-propanediol, which is probably a mixture of threo and erythro diastereoisomers judging by a comparison of its melting point with those of pure isomers.[8] However, the yield of this route was, again, not satisfactory.

The hydrogenation of α-oximino-β-ethoxypropiophenone by palladium in a mixture of acetic anhydride and acetic acid has been shown to afford α-acetamido-β-ethoxypropiophenone in a good yield.[2] Under similar conditions, parallel to this result, the reduction of oximinoketon (III) give a 90% yield of α-acetamido-β, β-dimethoxypropiophenone (IV). The hydrolysis of the acetal group of the latter compound IV by hydrochloric acid, did not, however, produce V in a good yield, the starting material being recovered. On the other hand, the treatment of IV with an aqueous alkaline solution afforded the desired hydroxymethylene compound, V, in an excellent yield. It is well known that the acetal group resists base-catalyzed hydrolysis. In this particular case, however, the seemingly anomalous hydrolysis by the base probably proceeds through a vinyl ether, which is a vinylog of ester, as is shown below:



The attempted hydrogenation of the hydroxymethylene ketone thus obtained resulted in the recovery of the starting meterial. The inertness to hydrogenation of the carbonyl group in V is probably due to the carboxylic group-like character of the -COCH=CHOH system.

Several examples of the successful hydrogenation of hydroxymethylene ketone to the corresponding diol by means of a Raney nickel catalyst have been reported.[9]

The reduction of V by this method afforded an excellent yield (90%) of the desired 1-phenyl-2-acetamido-1, 3-propanediol (VI). That the product was a mixture of approximately equal amounts of threo and erythro compounds was inferred from a comparison of its infrared spectrum with those of pure stereoisomers. From the product, the threo isomer was isolated through recrystallization, while the erythro isomer was separated as a triacetyl compound (47% based on the hydroxymethylene compound) after the treatment of the reaction product with acetic anhydride and pyridine.

A minor product of catalytic hydrogenation with Raney nickel was isolated in the course of separation; it had an elemental composition of $C_{10}H_{13}NO_2$ and was identified as 1-phenyl-2-acetamido-1-ethanol (VII) by comparison with an authentic specimen prepared by treating acetamidoacetophenone with sodium borohydride. The course which led to this product is obscure; it might involve the deformylation of the hydroxymethylene ketone by alkaline substances on the surface of Raney nickel.

Lastly, the reduction of enolacetate (VIII) was attempted. The enolacetate (m. p. 117°C) was readily obtained by treating the sodium salt of the hydroxymethylene ketone (V) with acetic anhydride under cooling. The acetate is very susceptible to alkaline hydrolysis, regenerating V. Acetylation without cooling gave a product, $C_{13}H_{13}NO_4$ with a m. p. of 130°C, this also regenerates V on alkaline

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[7] W. H. Hartung and Y. C. Chang, *J. Am. Chem. Soc.*, 75, 89 (1953).

[8] T. Taguchi, T. Tomoeda and T. Ishida, *Yakugaku Zasshi*, 75, 666 (1955).

[9] H. Rupe and O. Klemm, *Helv. Chim. Acta*, 21, 1538 (1938); B. D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, 77, 4079 (1955).

hydrolysis and exhibits an infrared spectrum consistent with an enolacetate structure. The compounds with m. p. of 117 and 130°C may, therefore, be cis and trans isomers of the enolacetate. The catalytic hydrogenation of the enolacetate with Raney nickel gave a 50% yield of an erythro compound *N*-acethylnorephedrine and 14% of acetamidopropiophenone. *N*-acethylpseudonorephedrine was not present in an isolable amount.

Experimental

Phenyl β-Chlorovinyl Ketone (I).—This compound was prepared by a modification of the method of Klinko et al. A mixture of 100 g. of benzoyl chloride and 100 g. of aluminum chloride was heated gently to give an adduct. The adduct was then dissolved in 200 ml. of tetrachloroethane. Dry vinyl chloride was introduced into the solution through an inlet tube reaching to the bottom of the vessel. A large test tube was employed as a reaction vessel in order to keep the gas in good contact with the solution. The vinyl chloride was then generated by the decomposition of 120 g. of dichloroethane with 150 g. of sodium hydroxide in 500 ml. of 60% ethanol. The temperature of the generating flask was adjusted so that the gas produced was effectively absorbed in the reaction mixture. It took 10 hr. for the reaction to be completed. After it had been set aside for several hours, the resultant solution was poured into a mixture of ice and dilute hydrochloric acid. The product was extracted with ether, and the extract was washed successively with dilute hydrochloric acid, twice with a 10% sodium hydroxide solution, and with water, then it was dried over sodium sulfate. After the removal of the solvent, the residue was distilled in vacuo. A pale-yellow viscous oil boiling at 124°C (12 mmHg) was collected; yield 93 g. (78.5%).

Benzoylacetaldehyde Dimethyl Acetal (II).—The general procedure described by Nelles[10] was used.

α-Oximino-β, β-dimethoxypropiophenone (III).—A solution of 5.8 g. sodium in 180 ml. of methanol was cooled in an ice-water bath and stirred. To this solution, 29.5 g. of isoamyl nitrite (or an equivalent amount of isopropyl nitrite) and 49 g. of acetal II was added successively. After it had stood for three days in a refrigerator, the light orange reaction mixture was poured onto ice water. The solution was then washed with ether three times. From this ethereal solution, 9 g. of unchanged acetal was recovered. The aqueous solution of the product was saturated with ammonium chloride and extracted with ether. The extract was dried over sodium sulfate, and the solvent was removed. The residual yellow paste was crystallized after being set aside for several hours. The crystalline cake was washed with a small amount of benzene and recrystallized from the same solvent; yield 20 g. From the benzene used for washing and recrystallization, a further 15 g. of the product was obtained by extraction with an adequate quantity of 5% aqueous sodium hydroxide, followed by saturation with ammonium chloride and subsequent extraction with ether (76%). The purified product melted at 86—87°C.

Found: C, 59.92; H, 5.37; N, 6.34. Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87, N, 6.28%.

The acetoxyimino compound was obtained as follows. A yellow solution of 500 mg. of the isonitroso ketone III in 4 ml. of 5% aqueous sodium hydroxide was shaken with a solution of few drops of acetic anhydride in 4 ml. of ether. The mixture was decolorized immediately. From the ether extract the product was obtained in a crystalline condition, m. p. 90—92°C. Yield 600 mg. (quantitative).

Found: C, 59.22; H, 5.97; N, 5.68. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28%.

The treatment of the oximino compound with benzoyl chloride gave the corresponding benzoyl oximino derivative; m. p. 63—65°C. Yield 95%.

Found: C, 66.15; H, 5.20. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24%.

Both acetoximino and benzoximino compounds were dissolved in 5% aqueous sodium hydroxide to give a yellow solution. The original oximino ketone III was regenerated by saturation with ammonium chloride and by extraction with ether.

The Catalytic Hydrogenation of α-Oximino -β, β-dimethoxypropiophenone (III). — a) Oximino ketone III (2 g.) was dissolved in a 3 N methanolic hydrogen chloride solution and hydrogenated in the presence of 400 mg. of palladium charcoal. After 3 mol. of hydrogen had been absorbed, an equal amount of water was added to the solution. The catalyst was then replaced by platinum oxide, and the hydrogenation was continued until 1 mol. of hydrogen had been further absorbed. The catalyst was then removed, the solution was washed with ether, and the aqueous solution was made alkaline with concentrated sodium hydroxide. The product was next taken up in ethyl acetate, and the extract was dried and evaporated to leave an yellow oil. The benzoylation of this oil by the Schotten-Baumann method gave a small amount of white crystals. The benzoate, recrystallized from ethyl acetate, melted at 204—207°C. The comparison of the melting point of this crystal with those described in the literature[8] indicates the product to be a mixture consisting of two diastereoisomers of 1-phenyl-2-amino-1, 3-propanediol tribenzoate.

Found: C, 75.09; H, 5.71; N, 3.33. Calcd. for $C_{30}H_{25}NO_5$: C, 75.14; H, 5.26; N, 2.92%.

b) Two grams of oximino ketone III in a 3 N methanolic hydrogen chloride solution were hydrogenated in the presence of 400 mg. of palladium-charcoal. After 3 mol. of hydrogen had been absorbed, the catalyst was removed and the solution was made alkaline by passing through gaseous ammonia. Ether was then added to the solution, and the precipitated ammonium chloride was removed by filtration. The evaporation of the solvent under reduced pressure at room temperature left a brown past which was treated with benzoyl

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[10] a) J. Nelles, Brit. Pat. 466890 (1937); *Chem. Abstr.*, 31, 7886 (1937); b) T. Matsumoto, R. Ishida and H. Shirahama, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 83, 147 (1962).

chloride under Schotten-Baumann conditions to give white crystals. The benzoate, recrystallized from methanol, melted at 155—157°C. The analysis indicated that the product was 1-phenyl-2-amido-3, 3-dimethoxy-1-propanol dibenzoate.

Found: C, 71.54; H, 6.20. Calcd. for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01%.

α-Acetamidohydroxymethyleneacetophenone (V). —a) A solution of 9 g. of the oximino ketone III in a mixture of 40 ml. of acetic acid and 40 ml. of acetic anhydride was shaken with hydrogen in the presence of 1.5 g. of 10% palladium on charcoal until 2 equivalents of hydrogen had been absorbed. After the catalyst had been removed by filtration and the solvent had been evaporated, the residue was vigorously shaken with 160 ml. of 0.5 N aqueous sodium hydroxide. The solution was washed with benzene, made acidic with 2 N hydrochloric acid, and extracted with benzene. The extract was dried and the solvent removed to leave the crystalline hydroxymethylene ketone V. The product, washed with ethanol and recrystallized from benzene, melted at 113—115°C. Yield 6.7 g. (81%).

Found: C, 64.58; H, 5.62; N, 6.88. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%.

b) The hydrogenation of 3 g. of oximino ketone was carried out in the manner described in a). The paste obtained after the removal of acetic acid - acetic anhydride, crude α-acetamido-β, β-dimethoxy propiophenone, was dissolved to a homogeneous solution by shaking it with 190 ml. of 2 N hydrochloric acid for 2 hr. The ultraviolet spectra of the resultant solution showed λ_{max} 251 mμ (ε 1030), whereas a solution of pure V in 2 N hydrochloric acid showed λ_{max} 251 mμ (ε 11400). Thus, in the reaction mixture only 10% of the original acetal was estimated to be converted to the hydroxymethylene compound. Since further treatment of the solution for 6 hr. did not produce any increment in the extinction coefficient, the solution was extracted with ethyl acetate. The extract afforded 0.3 g. of the desired V.

α-Acetamidoacetoxymethyleneacetophenone (VIII).—A solution of V in an equivalent amount of 0.5 N aqueous sodium hydroxide was overlayered by ether, and an equivalent amount of acetic anhydride was added portion by portion with continuous shaking and cooling. When the yellow color of the alkaline solution had disappeared, the ethereal layer was separated and dried. After the solvent had been removed, the crystalline acetate VIII was obtained in a good yield; m. p. 116—117°C.

Found: C, 63.47; H, 5.47; N, 5.60. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67.

An isomeric acetate was obtained as a colorless crystal which melted at 128—130°C when acetylation was carried out without cooling. Both acetates gaves red coloration with ferric chloride and were converted to the original aldehyde (m. p. 113—115°C) when treated with aqueous alkali.

Found: C, 63.35; H, 5.35; N, 5.52. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67%.

The Hydrogenation of V with a Raney Nickel Catalyst.—To a solution of 1 g. of the hydroxymethylene compound in 10 ml. of tetrahydrofuran, 1 ml. of Raney nickel was added. Hydrogenation at 100 atm. was carried out at room temperature. After the catalyst and solvent had been removed, the residue was dissolved in a small amount of ethyl acetate. Upon scratching the wall of vessel, a mixture of two diastereoisomers of 1-phenyl-2-acetamido-1,3-propanediol (m.p. 92—117°C, 310 mg.) was crystallized out. Recrystallization from ethyl acetate and then from ethanol gave the threo isomer (m. p. 134°C), whose melting point and infrared spectra were identical with those of the literature.

Found: C, 63.09; H, 7.53; N, 6.36. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69%.

The paste obtained from the mother liquor was chromatographed on a column of aluminum oxide by ethyl acetate. Fractions eluted at earlier stages contained 101 mg. (10%) of 1-phenyl-2-acetamido-1-ethanol, which was identified with a sample prepared by the sodium-borohydride reduction of acetamidoacetophenone.

Found: C, 67.98; H, 7.57; N, 7.78. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%.

The fraction eluted later contained 595 mg. of a mixture of the isomeric propanediols VI, bringing the total yield to 88.5%. For the separation of each diastereoisomer, the mixture was converted to a triacetly compound by treating it with acetic anhydride and pyridine. The *erythro* triacethyl-1-phenyl-2-amino-1, 3-propanediol (595 mg.; 47% yield based on aldehyde) thus obtained melted at 115—118°C. Both the melting point and the infrared spectrum were consistent with those of the literature.

Found: C, 61.07; H, 6.61. Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53%.

The Hydrogenation of α-Acetamidoacetoxymethyleneacetophenone (VIII).—One gram of α-acetamidoacetoxymethyleneacetophenone (VIII) in 5 ml. of ethanol was hydrogenated with 0.5 ml. of a Raney nikel catalyst at room temperature under a pressure of 50 atm. After 4 hr. shaking, the catalyst and solvent were removed to leave a pasty mass containing crystalline *N*-acetyl-norephedrine. The product (320 mg.), recrystallized from ethyl acetate, melted at 134—135°C. The mixed melting point determination with an authentic specimen prepared by a known process showed no depression. The noncrystalline portion of the product was dissolved in ether and chromatographed on aluminum oxide. A further quantity (75 mg.) of *N*-acetylnorephedrine was obtained (total yield, 46.7%). Besides, 165 mg. (14%) of α-acetamidopropiophenone and 105 mg. of a paste, the infrared spectrum of which was consistent with 1-phenyl-2-acetamido-1, 3-propanediol monoacetate, were obtained. In the reaction mixture *N*-acetylnorpseudoephedrine could not be detected.

1-Phyenyl-2-oximino-3, 3-dimethoxy-1-propanol (IX).—To a solution of oximinoketone (III) in methanol an excess of sodium borohydride was added. The reaction mixture foamed vigorously and became yellow. After 24 hr., the foaming ceased and the solution became colorless. The methanolic solution was evaporated to dryness, and the residue was dissolved in dilute aqueous sodium hydroxide and the product taken up by extraction with ethyl acetate. The extract was then dried. The removal of the solvent left a crude product which was recrystallized from ethyl acetate to give a pure sample (m. p. 83—85°C). The treatment of the product obtained above with acetic anhydride and pyridine gave an acetoxyimino alcohol (m. p. 83—85°C). A mixed melting point determination with the original isonitroso alcohol showed a distinct depression.

Found: C, 58.04; H, 6.14; N, 4.92. Calcd. for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53%.

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